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THE IMPACT OF STIMULANTS ON THE CARDIOVASCULAR AND METABOLIC RISKS IN ADULT PATIENTS WITH ADHD: EMPHASIS ON CHOLESTEROL PROFILE CHANGES

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ABSTRACT

Objective: The objective of this study is to examine the impact of central nervous stimulants on the cardiovascular and metabolic risks in adult ADHD patients. **Method:** Participated in this study, consenting male and female consecutive outpatients with confirmed ADHD diagnosis. All patients received either amphetamine or methylphenidate stimulant treatments for 12 weeks. The primary outcome measure included the lipid profile measures. Other clinical outcome measures included; resting heart rate, systolic and diastolic blood pressure, weight, BMI, fasting glucose, and HBA1C. Cholesterol profile measures and other cardiovascular risk measures were gathered once before the stimulants were initiated and 12 weeks after continuous treatment. Symptom frequency changes were measured by completing the "Adult ADHD self report scale - ASRS-v1.1" before and 12 weeks after treatment. The study was granted approval by the Conjoint Scientific and Ethics Board at the University of Calgary. **Results:** The paired t test, was utilized to examine changes in cholesterol and other cardiovascular risk variables. After 12 weeks of stimulant treatment, there was significant reduction ($p < .01$) in the LDL-C measure but there were no significant decrease in any of the other lipid measures, there was significant decrease ($p < .001$) in weight, and in BMI. There were no significant changes in fasting glucose, or in HBA1C parameters. Employing ANOVA, there was significant ($p< .001$) decrease in the ASRS-vi.i, self report scale scores at 12 weeks. **Conclusion:** Stimulants used in adults with ADHD are associated with minor, but statistically significant and favorable changes in the LDL-C lipoprotein. However, there was no significant changes in the overall cardiac risk as measured by the Framingham Risk Score (FRS). It is concluded from reviewing literature that the overall cardiovascular risk seemed to be dependent on number of factors, including but not limited to, genetic, environmental, biochemical factors, as well as on the interaction with other disease status variables.

KEYWORDS: Stimulants, ADHD treatment, Cholesterol, Cardiovascular, risk.

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is an early-onset neuropsychiatric disorder, with a prevalence rate of 5% to 7% of school-age children and 4% of adults, and with a male: female ratio of 3:1.[1,2] Several recent studies suggested an estimate between 30 percent and 70 percent of children with ADHD continue to exhibit symptoms in the adult years, and that ADHD in adults is mostly left untreated.[3] Untreated ADHD, unfortunately can adversely affect school and work achievements, diminish self-esteem, damage interpersonal relationships, and significantly reduce quality of life for adults.[4]

It is demonstrated in recent systematic reviews that central nervous system stimulants are more efficacious than placebo, and more effective than non-stimulant medications, and psychotherapy in the treatment of ADHD. Among stimulant drugs are the methylphenidate, and amphetamine group of drugs. However, most of the efficacious pharmacological treatments are associated with side effects, commonly anorexia, weight loss and insomnia. Stimulants in particular are associated with clinically minor, but often statistically significant changes in heart rate and blood pressure. Given these cardiovascular effects of stimulants, it became as a routine clinical practice to monitor patients' pulse and blood pressure at baseline and periodically during treatment.[5,6]

The impact of stimulant treatments on lipid profile, and on other metabolic changes

From literature review, contrary to central nervous stimulants, different psychotropic drugs such as antidepressants, and antipsychotics are extensively examined in published literature for their impact on lipid profile, on metabolic parameters and on the associated cardiovascular risks among psychiatric patients treated for depression and anxiety disorders. For example, Hiles et al 2016, demonstrated that antidepressant use was independently associated with higher triglycerides and lower HDL-C.[7- 9]

To the contrary to psychotropic drugs, very little is published about the impact of stimulants on cholesterol profile. However, authors identified only one published follow up study that examined the impact of the stimulant methylphenidate on lipid profile. Charach et al 2009, reported that Methylphenidate had favorable effect on plasma cholesterol profile after three months of continuous treatment including; significant decrease of total cholesterol, triglycerides, and LDL-C, in the plasma of adult patients diagnosed with attention-deficit ADHD. A through and extensive literature search did not reveal any other published studies of significance that examined the impact of methylphenidate or other stimulants on plasma lipid profile.[10]

Contrary to many psychotropic medication, stimulants used in treating ADHD are found to be associated with less appetite and at times resulted in significant weight loss. For example, Spencer et al 2006, reported that among the most common adverse events in adolescent patients receiving the mixed amphetamine salt (MAS XR) versus placebo were decreased appetite and weight loss.[7, 11]

The impact of the ADHD stimulants on the cardiovascular risk factors

The increase in death rates from heart disease has been strongly associated with increase in the prevalence of coronary atherosclerosis, associated with an increase in serum cholesterol levels. However, the decreased morbidity and mortality estimates from coronary heart disease over the past 30 years was best explained by the decreased incidence of acute myocardial infarction and a decrease in sudden death from coronary heart disease. This is best explained by decrease in coronary atherosclerosis due to primary prevention.[12]

There is strong evidence to suggest that lowering blood cholesterol reduces the risk of coronary heart disease, and the National guidelines were developed for lowering blood cholesterol to prevent heart disease. It was demonstrated in angiographic trials that cholesterol-lowering therapy will reduce progression of atherosclerosis and in some cases, will reverse existing lesions, especially in high-risk patients.[13,14]

The prediction of coronary heart disease using risk factor categories, the Framingham Cardiovascular Risk score (FRS)

Algorism models were developed to predict cardiovascular risk, which is dependent not only on cholesterol blood levels but also on other important risk factors. The Framingham Heart Study has been a leader in the development of multivariable statistical models to estimate the risk of coronary heart disease. The Framingham Cardiovascular risk score (FRS) is defined as the chance of having a heart attack or stroke over the next 10 years. The 10 year risk for developing coronary heart disease is calculated by utilizing algorithms based on different models which were formulated with age, and sex-specific equations to predict Coronary Heart Disease (CHD) risk, and taking into account the presence or absence of other major contributing health conditions such as, diabetes, smoking, blood pressure categories, the total cholesterol and LDL-C cholesterol blood level categories. Sullivan et al 2004, developed a points system, for making the complex statistical models easy to use, that does not require a calculator or computer and which can assist clinicians or motivated patients to estimate and monitor cardiovascular risk over time.[15]

In a large prospective 12 years population follow-up study which involved 2489 men and 2856 women 30 to 74 years old, patients' morbidity and mortality were significantly associated with categories of blood pressure, total cholesterol, LDL-C cholesterol, and HDL-C cholesterol. Sex-specific prediction equations were formulated to predict CHD risk considering age, diabetes, smoking, according to the Joint National Committee blood pressure categories, and according to the National cholesterol categories guidelines. Authors demonstrated that the guidelines of blood pressure, total cholesterol, and LDL cholesterol effectively predict CHD risk in a middle-aged white population sample.[16]

In conclusion, if we agree that stimulants may have favorable outcomes on lipid profile measures, as suggested by Charach et al 2009, one may expect an overall low cardiovascular risks in patients treated by stimulants. Therefore, the objectives of this study is set to examine changes in cardiovascular parameters, in metabolic risks, and in the overall cardiovascular risk, with emphasis on lipid profile changes in adult ADHD patients treated by central nervous system stimulants.

MATERIAL AND METHODS

Study design

This is a 12 week prospective follow up study to examine the impact of stimulant treatments including, Dexedrine and methylphenidate on the cardiovascular and metabolic risk factors, with emphasis on cholesterol plasma level changes in adult ADHD patients treated by central nervous system stimulants.

Therefore, this is a pre-post treatment follow up study, in which assessments were carried out at baseline (before

treatment started with stimulants and 12 weeks after treatment, to examine changes in the following dependent variables;

1) Cholesterol profile, as the primary outcome measures, including; (Total Cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), and triglycerides (TG).
2) The cardiovascular parameters including the resting pulse, systolic and diastolic blood pressure,
3) Metabolic factor changes including weight, Body Mass Index (BMI), fasting glucose**,** and the HBA1C,
4) Changes in the ADHD symptomatic after 12 week of treatment by stimulants, and
5) Changes in the overall Framingham Risk Score (FRS), at 12 weeks of treatment by stimulants.

The sample size

Considering the total cholesterol blood level as the primary outcome measure for cardiovascular risks, if 20% reduction cholesterol blood level would be a typical treatment response, and that the treated group would improve by 0.35 mol/lit points, and assuming that the standard deviation for the before-after difference (SD = 0.6) which was noted in other classical studies, and the desired power of 90%, alpha - 5%, then the required sample size is (n= 31), according to STATA.[17]

Inclusion -exclusion criteria

Adult patients (aged 19 -65) with the diagnosis of Adult Attention Deficit Disorder (ADD), were recruited from consenting outpatients who were referred to the clinic for treatment from ADHD. Excluded from the study, patients with chronic liver, renal or endocrine disease, or patients with eating disorders. Patients with acute psychiatric comorbidities such as patients with schizophrenia, bipolar disorders, major depressive disorders and suicidal patients or those with mental retardation, or other neurodevelopmental disorders, pregnant females, and patients prescribed ongoing cholesterol modifying drugs, were excluded. The diagnosis of ADHD was confirmed by fulfilling the criteria of the Mini-International Neuropsychiatric Interview.[18] The study was granted approval from the conjoint scientific and ethics board at University of Calgary.

Cholesterol measurements

Blood was drawn after an overnight fasting, and serum concentrations were assessed using enzymatic methods, for Lipid profile estimation of the 10 – 12 hours of fasting lipid profile. Samples for lipid profile included TC, LDL-C, HDL-C, and TG. The cardiovascular and metabolic measures believed to be critical in predicting coronary heart disease includes pulse, systolic and diastolic blood pressure, weight, lipid profile, fasting glucose, and HBA1C. All cardiovascular risk factors were measured on two occasions over time, once before treatment started, and after 12 weeks of continuous treatment. The 12 week period between the baseline and end-point measurements was considered as sufficient time to examine any change in the cardiovascular and metabolic risk factors that treatments with stimulant medication could have made.

Other outcome measures

The adult ADHD self report scale

The Adult ADHD self report Scale (ASRS-v1.1), Adler et al, 2006, is utilized to examine changes in the severity and frequency of the ADHD symptoms overtime.[19]

The Framingham Cardiovascular Risk Score (FRS)

The 10 year risk for developing coronary heart disease is calculated by utilizing the algorithm to predict CHD risk based on models which were developed with formulated sex-specific prediction equations and taking into account patient's age, the presence or absence of diabetes, smoking, blood pressure categories, and HDL-C cholesterol categories. The calculation of cardiovascular risk score requires information about the age, systolic blood pressure, TC and the HDL-C measures. For the purpose of this study, the cardiovascular risk score was calculated for each patient at baseline before treatment with stimulants and at 12 weeks of treatment utilizing the algorithm suggested by Wilson et al 1989.[16,20]

Patient follow-up

All patients were followed in an outpatient sitting. All patients were treated by stimulants, by either one of the amphetamine or one of the methylphenidate preparations, both of which are structurally chemically related. All patients were followed as outpatients to ensure tolerance and adherence to treatment, on a monthly basis. The stimulant dose was titrated gradually against tolerance and response to treatment in an open naturalistic fashion. Each patient remained on the same prescribed stimulant for the 12 week period of the study. Patients who were partially adherent and did not complete the 12 week of treatment or did not follow the protocol, were excluded from data analysis.

Data analysis

The paired t test, was employed to examine changes at 12 weeks, in the cardiovascular parameters (resting pulse rate, systolic and diastolic blood pressure), the metabolic measures (weight, BMI, Fasting glucose, and HbA1C), and lipid profile measures (TC, the high density lipoprotein HDL-C, the low density LDL-C, and TG). Analysis of variance (ANOVA) is used to examine changes in symptom frequency over time, as measured by the adult ADHD self report scale ASRS-v1.1, symptom checklist at 12 weeks.

RESULTS

A total of 50 consenting adult consecutive outpatients 19- 65 years old, with confirmed adult ADHD diagnosis fulfilled the DSM-IV diagnostic criteria of ADHD, and were enrolled in this study. However, out of the 50 patients, 43 completed the 12 week study with seven patients excluded due to partial adherence.

Table I. displays the demographic characteristics of those who completed the 12 week study. There were 27 males and 16 females (60/40 %), with a mean age 38.42. The age of participating males ranged from 33-42 (Mean / SD: 37.5(10.7), and the age of participating females ranged from 30-45 (Mean/SD: 40(9.1). All patients were non-smokers, non diabetic, and all patients did not have history of CHD or suffered from high blood pressure, and none had history of early death (<55 years), in the immediate family. All patients were treated by stimulants; including the pro-amphetamine stimulant "lisdexamfetamine" (n=31, 72%), the Mixed amphetamine salt (n= 4, 7%), and dexedrine SR (n= 5, 11.6%), or by methyphenidate (n=4, 9.4%). Methyphenidate is a piperidine derivative structurally related to amphetamines. Both amphetamine and methylphenidate drugs act as a central nervous system stimulant

Table 1. Displays changes in the cholesterol profile measures at 12 weeks of treatment by stimulants. There were non- significant decrease in TC, in HDL-C and TG lipids profile measures. However there was significant decrease ($p< 0.01$) in the mean (LDL-C) measure. There were no significant differences between males and females in any of the lipid profile or other cardiovascular risk factors.

Table 1: Changes in lipid profile among patients (n=43) treated by stimulants at 12 weeks.

GROUPS	95 % confidence interval difference			Significance	
Measure time	**M (SD)**	**Lower**	**Upper**	**T value**	**< p**
Total cholesterol (TC)					
Baseline	4.55(1.08)	-0.267	0.297	0.11	0.91
12 weeks	4.53(0.97)				
High density cholesterol (LDL)					
Baseline	1.52(0.59)	-0.117	0.222	0.62	0.54
12 weeks	1.47(0.42)				
Low density cholesterol (LDL)					
Baseline	2.70(0.94)	0.007	0.369	2.10	0.01
12 weeks	2.51(0.87)				
Triglycerides (Trig)					
Baseline	1/13(0.79)	-0.253	0.258	0.02	0.98
12 weeks	1.12(0.61)				

Paired t test $p< 0.5$

Table 2, displays the metabolic changes including body weight, the Body Mass Index (BMI), as well as the fasting blood glucose and HBA1C changes, at 12 weeks of treatment.

There was significant decrease in body weight ($p <0.05$) and in the BMI ($p< 0.01$) at 12 weeks of treatment with stimulants. However, there were no changes in fasting blood glucose or in the HBA1C measures at 12 weeks of treatment by stimulants.

There were no significant correlations between the ADHD symptom frequency and any of the lipid profile measures at baseline or at 12 weeks of treatment.

Table 2: Changes in the metabolic variables among patients (n=43) treated by stimulants, at 12 weeks.

GROUPS	95 % confidence interval difference			Significance	
Measure time	**M (SD)**	**Lower**	**Upper**	**t value**	**< p**
Wight					
Baseline	80.4(17.00)				
12 weeks	78.50(16.42)	-.12	4.04	1.90	0.05
BMI					
Baseline	27.78(4.76)				
12 weeks	26.78(4.76)	0.64	1.36	5.66	0.01
Fasting glucose					
Baseline	5.10(0.73)				
12 weeks	5.00(0.71)	-.19	.300	0.47	0.60
HBA1C					
Baseline	5.59(0.26)				
12 weeks	5.56(0.26)	-.030	.093	1.04	0.30

Paired t test, $p> 0.5$

Changes in the cardiovascular variables among patients (n=43) treated by stimulants, at 12 weeks

Table 3. describes the cardiovascular changes including pulse, blood pressure systolic and diastolic parameters. There was significant increase ($p < 0.001$) in the resting pulse rate, but there were no changes in the systolic or diastolic blood pressure measures at 12 weeks of treatment.

Table 3: Changes in cardiovascular and metabolic variables among patients (n=43) treated by stimulants, at 12 weeks.

GROUPS	95 % confidence interval difference			Significance	
Measure time	M (SD)	Lower	Upper	T value	< p
Resting Pulse					
Baseline	74.01 (9.89)				
12 weeks	79.5(9.99)	-0.8.31	-2.65	-3.94	0.001
Systolic Blood Pressure					
Baseline	124.0(13.01)	-4.45	2.35	-.63	0.5
12 weeks	125.0(13.44)				
Diastolic Blood Pressure					
Baseline	78.9(10.96)				
12 weeks	78.92(7.34)	-3.05	3.045	.00	1.0

Paired t test, $p > 0.5$

Table 4, summarizes the results of the calculated Framingham Risk Score (FRS), at baseline and at 12 weeks of treatment. The mean FRS scores remained low (< 20), at baseline and at 12 weeks of treatment by stimulants. There was only one 64 years old patient with a HDL-C measure of 1.04 who an FRS of 25 at baseline, which dropped to 18, at 12 weeks of treatment.

Table 4: Changes the Framingham risk score in patients (n=43) treated by stimulants, at 12 weeks.

GROUPS	95 % confidence interval difference			Significance	
Measure time	M (SD)	Lower	Upper	T value	< p
Framingham risk score, baseline	3.99(4.54)				
Framingham risk score, 12 weeks	3.78(3.53)	-.245	.668	.94	0.35

Paired t test $p < 0.5$

Table 5, displays changes in ADHD symptom frequency over time. There was significant ($p < .001$) decrease in the ADHD symptom frequency as measured by the adult ADHD self report scale, symptom check list ASRS-v1.1. These findings support the efficacy of stimulants in treating adults with ADHD.

Table 5: Changes Adult ADD symptoms among patients (n=43) treated by stimulants, at 12 weeks.

GROUPS	95 % confidence interval difference			Significance	
Measure time	M (SD)	Lower	Upper	P value	< p
*ASRS-v1.1, Baseline	47.28(12.32)	43.46	51.10		
ASRS-v1.1, at 4 weeks	36.93(13.50)	32.73	41.12		
ASRS-v1.1, at 12 weeks	30.86(12.90)	26.85	34.86	7.20	0.001

ANOVA, repeated measures $p < 0.5$

* ASRS-v1.1 scores: The adult ADHD self report scale (ASRS-v1.1) symptom checklist

DISCUSSION

The objective of this study was set to examine the cardiovascular and metabolic risks among adult ADHD patients treated by stimulants. The study was conducted in a prospective 12 week follow up fashion, in which patients acted as their own controls. Forty three patients submitted to the required laboratory tests of the study protocol and completed the 12 week study.

Changes in lipid profile findings

There was an emphasis in the current study on the impact of the ADHD stimulant treatment on cholesterol profile measure changes among adults treated by amphetamine salts, or methylphenidate preparations.

Thorough literature search identified a publication that has examined the impact of treatment by the central nervous stimulant methylphenidate on plasma cholesterol profile among adult patients with ADHD. In this study, Charach et al 2009, demonstrated that Methylphenidate significantly decreased majority of cholesterol profile measures. Authors reported that the median total cholesterol count decreased by 9 mg/dL ($P < .0002$),

LDL‑C decreased by 5.0 mg/dL (P < .016), and triglycerides decreased by 8.0 mg/dL (P < .016).[10]

Finding from the current study demonstrated that there was significant decrease in the LDL-C plasma levels only. There were non-significant reductions in the total cholesterol, HDL-C and triglycerides, at 12 weeks. These results are partially consistent with Charach et al 2009, findings. Authors are not aware of other studies that have examined the impact of treatment by stimulants on lipid profile. However, the significance of changes in lipid profile associated with the use of central nervous stimulants should be examined in the light of other cardiovascular risk factors.

The impact of ADHD psychiatric comorbidities on lipid profile

It is well documented that ADHD and anxiety disorders occur together in 25 – 30 % of patients (kessler et al., 2006).[1] Several published studies have examined the impact of other psychiatric disorders including mood disorders and psychotropic drug treatments on plasma lipid profile. For example, in a literature review, Papakostas et al 2004, identified abnormalities in serum cholesterol levels in patients with mood and anxiety disorders as well as in suicidal patients. However, current literature remain controversial and the biological significance of these abnormalities remains to be clarified.[21] Glueck et al, 1994, repotted that children hospitalized with affective, adjustment, disruptive, anxiety, and organic psychiatric disorders had higher triglyceride values than controls.[22] In the current study authors excluded from entering the study, of patients suffering from acute comorbid major psychiatric disorders.

The impact of genetic and life style factors on cholesterol profile

Early twin studies were interpreted as supporting the hypothesis that levels of plasma cholesterol were strongly influenced by genetic factors. However recent studies suggest that there is interplay of the genetic, the life style and other environmental factors such as dietary factors and exercise. Santos et al, 2014 indicated that many individuals with familial hypercholesterolemia phenotype have polygenic instead of monogenic cause of their elevated LDL-C concentrations, and individuals with familial hypercholesterolemia show elevated burden of subclinical atherosclerosis. [23] Also, most recent genetic studies demonstrated that there is a complex relationship between the role of genetic versus environmental factors in controlling cholesterol blood levels. For example, Balder et al 2018, demonstrated in a randomized clinical study that patients with a healthier lifestyle were not necessarily associated with low LDL-C in women without genetic predispositions.[24]

The impact of stimulant treatments on resting pulse and blood pressure

It was demonstrated consistently that stimulant such as amphetamine salts, and methylphenidate preparations to be associated with minor, but statistically significant changes in heart rate and blood pressure that were often observed in those receiving placebo.[25]

For example, Donner et al 2007, demonstrated significant elevations in most cardiovascular hemodynamic parameters, including resting pulse rate, systolic and diastolic blood pressure as a result of stimulant medications in children with ADHD. Authors concluded that this potential cardiovascular risk should be balanced against the beneficial behavioral effects of this class of medication.[26] Also, in a recent review, Stiefel and Besag 2010, indicated that amphetamines appear to cause minor increases in resting heart rate and blood pressure over the long term. However, there is growing evidence to suggest that amphetamines do not cause statistically or clinically significant increases in QTc. There is no clear evidence to attribute sudden death to stimulants.[27]

In the present study, there was significant (p < .001), increase in the resting pulse rate. However, there were no significant changes in the systolic or diastolic blood pressure at 12 weeks of treatment, which is consistent with the previously published research. Wilens et al, 2005 recommended that adults with ADHD should have their blood pressure and heart rate checked at baseline and periodically during treatment.[6]

The impact of stimulants on weight, BMI and other metabolic parameters

It is demonstrated in the current study that there was significant decrease in weight and in BMI scores after 12 weeks of treatment by stimulants.

These findings are consistent with other research findings. For example, Spencer et al 2006, reported that among the most common adverse events in adolescent patients receiving the mixed amphetamine salt (MAS XR) versus placebo were anorexia/ and decreased appetite, and weight loss.[11] It could be argued that treatment with stimulants may act as a protective factor against overweight due to its association with reduction in appetite, and which in turn may reduce the negative cardiovascular metabolic consequences. These claims should be examined critically in future studies in the light of recent research, taking into account the impact of ADHD illness on the overall cardiovascular risks. For example to the contrary Egbert et al 2017, demonstrated that ADHD symptoms were significantly associated with objective binge eating and with subjective overeating suggesting that some symptoms such as impulsivity are underlying the associations between ADHD symptoms, and these eating disorders, which may carry high risks.[28] As a matter of fact, despite weight loss and low BMI in adults treated by stimulants, findings from recent

studies demonstrated that ADHD patients are at a high risk of medical co-morbidities associated with eating disorders and some features of metabolic syndrome. Weight gain which is associated with the use of many psychotropic medications may have serious long term increased health risks, morbidity and mortality associated with high blood pressure, coronary heart disease, stroke, high cholesterol and diabetes mellitus.[7] Bogers et al, 2007and others demonstrated that even with moderate overweight, there is a significant increased risk of coronary heart disease independent of the traditional cardiovascular risk factors, hypertension, heart disease, colon cancer, and stroke.[29-31]

Other metabolic risks associated with Attention Deficit Disorder (ADHD)

The metabolic syndrome refers to the co-occurrence of several known cardiovascular risk factors, including insulin resistance, obesity, atherogenic dyslipidemia and hypertension. It identifies a subgroup of patients with shared pathophysiology who are at high risk of developing cardiovascular disease and type 2 diabetes.[32] Independent of the administered stimulants, the association of ADHD with obesity, diabetes, and hypertension have been ascertained. It is suggested that there are several complex contributing factors that make individuals with ADHD at a high-risk group for cardio-metabolic complications. For example, in a recent extensive review, Landau, 2019 concluded that ADHD is considered a risk factor for components of the metabolic syndrome, particularly obesity, type 2 diabetes mellitus, and hypertension both in adults and youth.[33]

In the current study, there were no significant changes in the fasting blood glucose and HBA1C, at 12 weeks of treatment by stimulants.

Number of investigators reported high prevalence rates of psychiatric disorders among ADHD patients, especially anxiety and depression, among metabolic syndrome patients. Few investigators examined the prevalence of other psychiatric disorders especially anxiety and depression among metabolic syndrome patients.[34] For example, Hiles et al, 2017 recently reported that antidepressants use were independently associated with higher waist circumference, triglycerides, and lower HDL-C, and other metabolic syndrome abnormalities. Symptom severity and antidepressant use were associated with subsequently increased number of abnormalities such as glucose abnormalities after 2 years of treatment.[9, 35] Also, Olguner Eker et al 2017, found that there was an increase in waist circumference and TC and HDL cholesterol levels, whereas there was a decrease in fasting blood glucose levels with treatment in patients using SSRI antidepressant escitalopram.[36]

The Framingham Risk Score (FRS)

One of the important objectives of this study was to examine the impact of the central nervous stimulants dexedrine salts and methylphenidate preparations on the overall cardiovascular risk, utilizing the FRS which measures the 10 year risk for developing coronary heart disease utilizing algorithm to predict CHD risk based on models with formulated sex-specific prediction equations and taking into account patient's age, the presence or absence of diabetes, smoking, blood pressure categories, and HDL-C cholesterol categories.[16] Lloyd-Jones et al 2003, examined all Framingham Heart Study participants examined from 1971 through 1996 who did not have CHD and were not receiving lipid-lowering therapy. Authors found that lifetime risk of CHD increases sharply with higher total cholesterol levels for men and women at all ages.[37] and Jahangiry et al 2017, found that high systolic blood pressure and fasting serum glucose were potent determinants of intermediate and high risk CVD risk of FRS scoring compared with low risk group ($P < 0.05$).[38]

In the current study, the mean FRS scores remained low before and after treatment, and there was no significant ($p< 0.35$) change of the FRS after 12 weeks of treatment. The low mean Framingham Risk scores (FRS) demonstrated in the current study before and after treatment with stimulants, are best explained by the overall strict selection criteria for inclusion in the study, in order to examine selectively the impact of stimulants on cholesterol profile, independent of other cardiovascular risk factors. All patients with endocrine disease, diabetes, eating disorders, obesity, hypertension, and high blood pressure, were excluded from this study. Also, patients included were non-smokers, all had low mean age in both males and females, all had no history of coronary heart disease history, and no patient had history of sudden death in their family from coronary heart disease.

On reviewing recent literature, number of investigators claimed that the FRS estimates, may not precisely predict or may over-predict the actual risk. For example, Lloyd-Jones et al 2004, argued the Framingham 10-year CHD risk prediction model may not identify subjects with low short-term but high lifetime risk for CHD, likely due to changes in risk factor status over time,[39] and others investigators found that the Framingham Risk Score Equations significantly overpredicted the actual risks of atherosclerotic cardiovascular disease events in a large Canadian population sample.[40] Also, Nishimura et al 2014, claimed that the FRS overestimated the 10-year risk of CHD for the Japanese population.[41] Authors suggested that there is need for further refinement of cardiovascular disease risk prediction scores that may differ from one culture to another, and recommendations are made for further work to generate multivariate risk models that can reliably predict lifetime risk for CHD.

CONCLUSION

In conclusion, the current study supports the findings that there are minor but statistically significant and changes in lipid profile parameters associated with stimulant ADHD treatments especially in the LDL-C lipoprotein.

The clinical significance of these findings should be examined critically in the light of larger controlled studies. If we agree that stimulants may have favorable outcomes on lipid profile measures, one may expect an overall low cardiovascular risks. However, recent research The findings from the current study are consistent with findings from a previous research study, which found that the stimulant methylphenidate treatment was associated with favourable lipid profile. However, treatment with the central nervous stimulants Methylphenidate or Dexedrine medications in this study, did not have significant change in the overall cardiovascular risks, as calculated using the Framingham Risk Score. The nature and mechanisms of determining the cardiovascular and metabolic risks in patients with ADHD are quite complex. It is demonstrated in recent literature reviews that multifactor mechanisms were hypothesised to explain lipid changes and explain their impact on the overall cardiovascular risk. These factors may include but not limited to genetic, environmental, iatrogenic, biochemical and interaction with disease status variables. Further studies are needed to critically examine literature findings in the light of objective and large controlled trials.

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Declarations

The preliminary results of this project was presented at the 2018American Psychiatric Association

Ethics approval

The conjoint scientific and ethics board of the University of Calgary granted approval for the study.

Authors' contribution

Adel Gabriel contributed to the conception and design, acquisition of data analysis, the presentation of data, and drafting the manuscript. Mr. Ryan Lam, and Drs Mona Nematian, and Mohib Basta contributed to data collection and entry.

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Conflicts of interest

The Author(s) declare(s) that there is no conflict of interest'.

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